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DISEASES OF THE NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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DISEASES of the NERVOUS SYSTEM

A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

Sibling Rivalry

RAYMOND W. WAGGONER, M.D.

Ann Arbor, Michigan

In view of the tensions and strife which plague the world today, it seems timely to discuss one of the oldest problems of which we have authentic record. The story of Cain and Abel is a symbol of the problem and should be a lesson for us in these troublesome times. Let me present a few of my thoughts on the topic of "Sibling Rivalry."

Bossard calls attention to the fact that the youngest child grows up in an increasingly complex family situation for not only the parents, but the other children as well, in the inter-play of their personalities exert their influence upon this child. Thus, even with only the ordinary differences in personal traits, the situation becomes extremely complex. Writing on this subject Bossard remarked:

"All hurts, humiliations, disappointments and frustrations experienced by the oldest child can be taken out on the younger brother and sister. This seems to be a universal healing process. Fathers who are bullied by employers turn sadist with their children. Women, brow-beaten by their husbands, become the terrors of their children. It is a healing process to pass pain along." Concerning the behavior of young children in the same family, Weill indicates that, "Even with wise parents, there is a tendency to prolong the last babyhood. The parents are older, their financial position is generally stronger, the cultural opportunities open to this child are constantly greater than those afforded the older children. Discipline may break down with him largely or completely."

James Plant treated the topic in his book, "The Envelope," commenting as follows:

"There are three distinct levels at which the conflict of sibling rivalry has carried through. On the first is the struggle with the brother and sister in the child's search for belongingness. On the second is a somewhat later struggle with siblings in the field of adequacy which is in part a carry-over from the earlier struggle and in part a training school for the competition of adult life." His third level does not seem particularly applicable to our present discussion. He suggests further, "Its present prevalence and sharpness bring a steady stream of patients to the psychiatrist who never ceases to be amazed at the extent of their disturbance over the bitterness of their emotions. Perhaps the importance of security is so great that few can afford to contemplate anything that threatens it."

We are all familiar with the regressive behavior which may occur in a child at the birth of a younger sibling. The older child observes the attention given to the new born and it is natural for him to regress to earlier ways of behaving in order to demand the attention that he no longer receives and which is now given the new arrival. It is natural also for the child to behave in an aggressive and hostile fashion toward the younger sibling—how applicable some of these mechanisms may be in our professional life.

However, this reference to family siblings is the symbolic rather than real focus of my attention. The rivalry which I propose to discuss does not have to do with blood siblings, but with professional siblings. Although psychiatry is one of the older

Presidential address delivered at the meeting of the Central Neuropsychiatric Association, Nashville, Tennessee, October 17, 1952.

branches of medicine, it underwent a kind of re-birth at the turn of the century and since that time has made rapid progress, not only in scientific development in a difficult and abstract field, but also in its position in the minds of the public. As a matter of fact, in many areas, psychiatry has been oversold. Promises of what can be done have sometimes far out-distanced reality.

Many of our professional siblings have recognized this and used it as a spring-board from which to express hostility and aggression, as a child reacts with hostility to what he regards as the intrusion of a sibling with whom he has to share attention. Bartemier quotes a participant at a conference on graduate education in clinical psychology, "Psychotherapy is an undefined technique applied to unspecified problems with unpredictable outcome. For this technique we recommend rigorous training." Although this remark was made in jest, it is clear evidence of the attitude of many of our colleagues. Some sixty years ago, a member of the University of Michigan Medical Faculty said, "The Department of Nervous and Mental diseases was well received by other departments but with 'A chip on the shoulder.'" Even now applicants to medical school have told me that they hesitate to indicate interest in psychiatry for fear of a prejudiced attitude toward their application.

Since minor personality disturbances are almost universal and since psychiatrists are presumed to know about such disturbances, it is not difficult to understand why the associates of psychiatrists may neutralize their insecurity by some sort of aggressive reaction. When threatened, our reaction is likely to be one of aggression and hostility toward the person we consider responsible.

One of my colleagues suggested to me the other day as we were talking about the subject that the time to lay the groundwork for a better inter-relationship of physicians should be in medical school, and to this I am sure we will all agree. But this is like saying that the foundation of good personality structure should start in the home. This is a truism but often difficult to bring about. Often "parents" in medical schools are not as broadminded, tolerant or understanding as we might hope them to be. Recently I was asked to see a patient who was being treated by an outstanding internist. This woman had a marked hypertension, had many personal problems, and was reacting to her difficulties by over-indulgence in alcohol. After seeing the patient, I reported my findings to the internist indicating that much of her difficulty was on an emotional basis. The internist seemed to be in agreement that even the patient's hypertension was largely the result of her emotional conflicts. I suggested that the patient have psychiatric treatment and agreed to make the necessary appointments for the patient. Before the first appointment the internist telephoned cancelling the arrangements for the patient stating his belief that the patient was able to handle her problems, although her difficulty had in fact incapacitated her for more than two years. Later the patient's daughter reported that the internist had indicated to her mother that she had no need of psychiatric help. It was for this reason that the psychiatric consultations were cancelled. I am sure that the suggestion of the doctor had been misinterpreted but since the patient had agreed to psychiatric help, there must have been something in the internist's attitude that fortified the patient's resistance to help. The patient has already returned to drinking.

Such opinions expressed by medical men in high position and authority do influence associates and assistants as well as students. Thus the attitude of destructive competition and rivalry are reinforced.

Will Menninger has emphasized the problem in quoting a statement of Allan Gregg:

> "The greatest unpleasant surprise of the war for medical men was the importance of psychiatry and psychology, and yet so inconstant, evasive or preoccupied are the majority of men that this greatest lesson can be disputed, evaded and soon forgotten."

Although the psychiatrist should be closely related to all medical specialties there are certain professional groups which are much more closely associated with him. The psychiatrist should and frequently does relate most closely to the neurologist. I was particularly impressed by this excerpt from an address by Dr. Walter Schaller at the

American Neurological Association meeting in 1946:

"There has been a general misconception of the role of neurology in medicine. Your dictionary defines Neurology as 'The sum of knowledge regarding the nervous system both in health and disease.' Thus defined, Neurology is a much broader concept than either Psychiatry or Neuro-surgery.

"Since Plato, it has been generally accepted that one may not separate the mind and body. However, one is led to conclude that this has not been particularly dominant in Psychiatry. Perhaps this is because of the deep-seated social traditions of the spiritual on one hand and the corporeal on the other. In this connection, I am speaking of the comparative neglect, or at least lack, of emphasis placed on heredity and constitution in the evaluation of psychic disorders, especially as to prognosis and therapy."

Schaller accuses psychiatrists of the very attitude which most of us at least consciously try to avoid, the separation of psyche from soma, and yet none of us, I am sure, will contest the fact that there is some truth in his statement. Sometimes the psychiatrist does become over-enthused about the emotional to the exclusion of the somatic factors. Better not to separate the soma from the psyche or to stress one more than the other.

In contrast Adolph Meyer in an address before the same association in 1922 argued for the use of the term Neuropsychiatry and for a closer association and more coordinated functioning of these two specialties of medicine. Schaller asserts that the word Neuropsychiatry is poor terminology and should not be used. He suggests that the contribution of Freud is limited to his emphasis on sex. To quote further:

"In fact, such designations as the falsely applied œdipus complex, libido fixation, phallic symbolism and the like are well on their way to psychiatric oblivion."

A positive manifestation of the rivalry between the neurologist and the psychiatrist is expressed in an article by Wilson and Rupp from which I quote:

"Chief among the Cassandras anticipating the early demise of the clinical Neurologist is his colleague, the so-called 'pure' psychiatrist, who though intoxicated with grandiose dreams about curing all the political, marital, martial, racial and economic ills of a sorely troubled world by the application of psychiatric principles is still unable to maintain a tolerable harmony amidst his own ranks. So preoccupied have some psychiatrists become with the broader sociologic, political and even mystic attributes of their specialty that they would divorce themselves entirely from any allegiance to medicine.

"Evidence that these opinions are not isolated idiosyncrasies is to be found in the agitation on the part of many psychiatrists that it is unfair to demand even the most elementary knowledge of clinical neurology and its related basic sciences of their younger disciples who are seeking certification as specialists. They see nothing incongruous in a psychiatrist so neurologically naive that he considers the red nucleus some mysterious appendage of the U.S.S.R."

In a summary, these authors sagely state that further progress requires coordinated team-work of the clinical neurologist, the psychiatrist, the internist, the neuro-surgeon, reinforced by the cooperation of the neuro-anatomist, the neuro-physiologist, the neuro-pathologist, the biochemist and workers in other basic sciences. In spite of this common sense conclusion they must needs take a last jibe at the psychiatrist:

"Let the psychiatrist postpone his fortuitous advice regarding the cures of the ills of the body politic until such time as he has more effectively mastered the causes and treatment of the mental ills of the individual patient. Let him abandon the hustings and return once more to the clinic and the laboratory."

While the psychiatrist is not entirely without blame, it is certain that he is frequently pressured into compromising situations by his colleagues who fear that he may have some knowledge which they should but do not have or by the awareness of their own emotional inadequacy. Thus it becomes necessary for them to criticize and "joust at windmills" as a mechanism of defense. An example of this kind of attitude within the ranks of psychiatrists is indicated in a letter to the editor of the American Journal of Psychiatry concerning Karl Menninger's book, *Mental Status*.

"However, one should not be so carried away by enthusiasm for this method as to confuse the disease with the medicines used to cure it. Houses suffer from parasites, not from the insecticide used to remove them. People suffer from pneumonia, not from 'penicillinitis,' 'Aureomycinitis,' or some such monstrous entity. Similarly, one should not properly speak of a neurotic with too strong a tie to the mother as having an œdipal relation to her, when one means that stifling parent-child emotional ties can sometimes be made to lose their cogency,

that is, can be deconditioned, if successfully infiltrated with incest horror. The œdipus complex, to take by way of illustration one tool in the armamentarium of the psychoanalyst, so to speak, which the patient's 'unconscious' and with the therapist's willing help, arises to combat the roots of the neurosis, so to speak. Psychoanalysis is a fairly fixed and systematized process of deconditioning, whereof the 'sting,' as Freud termed it, lies in those 'free' associations, i.e., in those negatively toned associations, memories, and fantasies that are directed against the roots of the neurosis. Whether we are dealing here with scientific cause and effect or some sort of ortho-psychiatric poetry, has not yet been established."

Menninger's response to this criticism is clear and well taken. Martin Luther has given us an applicable epigram, "It makes a difference whose ox is gored."

Regressive behavior is a common form of reaction and when the older sibling sees attention being given to the new born, it is natural for him to return to infantile ways of behavior. It would appear to me that some of the material which I have quoted might well be symbolic of such regressive behavior. Lest I should be accused of negative interaction because of some of the references I have used, I hasten to add that I do believe in the causality of human behavior, that therefore there must have been good reason for such abreaction on the part of the authors quoted.

Another approach to the relationship between neurology and psychiatry is indicated by Dr. Pierce Bailey in a paper he read at the proceedings of the American Neurological Society in 1950, "Should the term Neuropsychiatry be Scrapped?" He discusses the history of the term, points out that during World War I most of those in charge were neurologists, but that in World War II, the psychiatrist was favored. He points out that many heads of departments of neuropsychiatry in medical schools are psychiatrists and he asserts that the term neuropsychiatry and psychiatry have come to be considered synonymous. It is his suggestion that the use of the term appears to be of no advantage to psychiatry and detrimental to neurology. He suggests that the acceptance of the psychogenic theory of disease has inactivated the dogma that a psychiatrist must be basically neurologically trained and that neurologists, by accepting the term neuropsychiatry, have at least partially lost their identity as neurologists and are being eclipsed by a large rising generation of psychiatrists. Thus, unity is being weakened. Even in this article, there is still the bugaboo that the discipline of neurology may be overwhelmed and absorbed by the discipline of psychiatry.

It is not my purpose to debate the issues raised by the articles from which I have quoted although I must confess that in some there is a distinct flavor of absurdity. Instead it seems important to attempt constructive progress in overcoming such useless sibling rivalry. Certainly little is to be gained by such polemics. Let us not be either Cain or Abel.

It would seem pertinent to examine some of the dynamics which might be operative in producing this situation. Bertrand Russell says, "It is preoccupation with possession more than anything else that prevents men from living freely and nobly." As Adolph Meyer has pointed out, "Psychiatrists and neurologists cast their lot together in a remarkable unitary organization during World War I." We can band together to overcome a common problem, but when the overwhelming threat is removed or reduced, then the bickering among ourselves tends to recur. Perhaps partly because it is dealing with something so abstract as the mind, the psychiatrist tends to be set apart from his siblings and unfortunately sometimes sets himself apart. Our colleagues are often influenced by public opinion and public opinion can be prejudiced. Money-Kryle has defined prejudice as an "opinion influenced by unconscious motives and beliefs which would be different if these were conscious. Our judgment may frequently be influenced by prejudices of which we are consciously unaware." With the advent of strong drives toward socialized medicine, medical men must better understand their relationship to each other or they may well bring about that which they most want to avoid. The medical profession is threatened from within as well as from without, by rivalries and antagonisms, by hostility and aggression.

An interesting study is under way by the Research Center for Group Dynamics at the

University of Michigan directed by Dr. Alvin Zander. The original group consisted of 156 psychiatrists, 165 clinical psychologists, and 159 psychiatric social workers. I think it would be well to quote from an introductory statement made by Dr. Zander:

"For a long time it has been accepted that the role which one occupies automatically defines his relationship to other persons. If you or I were to walk about town in a policeman's uniform, for example, we would elicit behavior from persons on the street which would be quite different from that directed toward us in our ordinary dress. The role occupied by you or me and the role held by others are said to exercise an important influence on the type of relations we set up with each other. A primary interest in the investigation was a curiosity about the psychological factors involved in the relations among persons occupying different roles. It is a common occurrence that mis-perception, misunderstanding, dependency, undue cordiality or other affect latent reactions occur among persons in different occupational groups, where these occupational groups have overlapping functions within the same social setting. Architects have trouble with contractors, personnel officers and line officials often disagree, psychiatrists offend ministers and visa-versa. Often these problems arise because the persons concerned have different goals and thus pull in opposite directions. Just as often, perhaps, and more puzzling, is the case in which persons with different roles share the same goal and develop attitudes and behavior toward each other which create friction in their working relations."

Zander uses "role" as a pattern of functions which are assigned or expected by a group because these functions are important to the group. Thus the role is not necessarily the same as the occupation. Persons in separate occupational groups may possess unique functions which others never perform or may have some functions which are widely shared or hoped to be shared by others. In order to carry out these functions the individual inter-acts with other people in a complex situation. Zander defines or analyzes the inter-actional situation in terms of what he calls dimensions, examples of which are: Rivalry with, power relationship with, dependent upon, helpful to, contact with, and so forth. From their study, it appears that the dimension, "power relationship," was most important. Zander concludes that it is possible to anticipate with some success the effect of "power relationships" and satisfaction using a theory of threat orientation and security. Thus difficulties in inter-relationship might be considered on the basis of anxiety generated by insecurity.

As Money-Kryle says:

"The ultimate source of persecutory anxiety may be obscure, may be a reaction to threat to self from something inside self. If our own fears were reduced to realistic proportions, so would be our hate. Under the influence of his own anger, the child's world may become hostile and dangerous in a wholly unrealistic way. He feels threatened by enemies who are projected representations of his own aggression and these become yet more dangerous in proportion to his efforts to defend himself against them."

To the internist, or the surgeon, the "unconscious" is something outside his normal frame of reference and therefore may well be the source of anxiety. Psychiatric teaching in medical schools has, in the past, been inadequate with the result that many physicians do not understand psychiatric concepts—what we don't understand, we don't like. However, I should like to reemphasize that the psychiatrist is not without fault when he allows the patient or his medical confreres to invariably expect a personality transformation by long term psychotherapy or psychoanalysis. Unrestrained and inaccurate discussion of medical problems frequently leads to misunderstanding whether this be the gasconading of the psychiatrist to the internist or the braggadocio of the surgeon in a social group. Many patients expect much more than can be accomplished and, unfortunately, they are not set straight by the psychiatrist or psychoanalyst. Sometimes, too, our medical siblings do an overzealous job of selling what we or they can do for a patient.

Whatever the mechanism of professional sibling rivalry may be, the important thing is the development of some means of overcoming it. As one of my friends said, it seems wise to start very early in the medical schools. Here the occurrence of prejudicial attitudes, mocking comments and innuendos made by our medical colleagues concerning each other increases the difficulty of teaching, tends to prolong the psychological "inheritance" and emphasize the rivalry between medical groups. Students tend to follow or introject the attitudes of

their more positive teachers. Psychiatry is less concrete and more difficult to comprehend than other fields of medicine; thus it threatens the student and tends to reinforce these opinions. It becomes necessary, therefore, to neutralize the fears and anxiety of the student, to give him as much support as is possible during medical school and to help him to realize that the threat can be overcome by understanding.

As Russell has said, "Knowledge and human power are synonymous, since ignorance of the cause prevents us from taking advantage of the effect." We should not overemphasize the extent of our knowledge nor minimize it. At the same time, we should try to counteract the aggression of our colleagues by positive measures, not by expressions of our own hostility.

In the same vein Will Menninger remarked: "The group is only protective of and helpful to and profitable for its individual members as the average level of psychological maturity of that membership permits." By our own hostility and aggressiveness, we only prolong the vicious spiral of criticism and innuendo, even though such reaction may be the result of our own insecurity and blind aggressiveness expressed without mature judgment. No one will question that favorable attitudes are more easily destroyed than created.

One of the best examples of a change of attitude on a large scale occurred in military service during the last war, resulting in a planned program of education and understanding initiated in the psychiatric consultant's office under the leadership of Will Menninger in the Army and Braceland in the Bureau of Medicine and Surgery of the Navy.

The development of liaison programs based on more than only mutual understanding and cooperation will most certainly lead to better professional relationships. The patterns of our relations with our younger associates will go far in developing the normal sibling aggressiveness into significant positive rather than negative outlets. Unfortunately psychiatrists are not sufficient in number and sometimes not in skill to give the service that may be demanded. This fact must be presented clearly and frankly to our colleagues and the public in order that we may not be forced to accept assignments that we are unable to fulfill, but we should meet the responsibilities that our confreres may justifiably expect. Although a psychiatrist has a right to have the same kind of personality-reaction as anyone else, yet by the nature of his training, he should have a deeper and more thorough comprehension of human foibles and thus he should be in a position to lead his medical siblings in the fight against prejudice and misunderstanding.

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The Frontal Lobes

(A Review of the Literature)

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Cerebral Organization

Before beginning our discussion of the frontal lobes it should be emphasized that the brain is a unified whole. Its functions are dependent on dynamic interrelationships of both cortical and subcortical structures, as pointed out by Sherrington.[84] Since it is easier for us to conceive of static categories than of relations in flux, we are constantly in danger when considering the brain, of thinking of compartmented functions and discrete centers. These concepts serve a useful function in description, and taken in the proper perspective, have a certain validity. Penfield and Rasmussen,[71] for example, have shown that one can localize function more or less discretely on cortical stimulation, e.g. stimulation of a given point on the temporal lobe of a certain patient repeatedly gave rise to the same 'dream' experience. Such organized neuronal patterns, if any, however, are subject to modification. Glees and Cole[35] outlined discrete areas of the motor cortex (e.g. the hand area) of a monkey by stimulation and ablated it. There was a temporary paralysis, followed by complete recovery. Craniotomy was repeated and stimulation of previously 'silent' areas in the adjacent cortex elicited precise (hand) movements. This is a careful demonstration of what must occur clinically in recovery from traumatic aphasia, from the paralysis following 'C.V.A.,' etc. (cf. also 49). The mechanisms of this functional reorganization are not clear, but Langworthy[50] for example, has shown that myelination (and presumably functional maturity) of the central nervous system of kittens and children is dependent on use. This functional plasticity of the nervous system must compensate in some degree for its poor regenerative powers.

Also important is the functional interdependence of various parts of the brain as indicated by the interrelations of the electrical records from the cortex, the basal ganglia, and the thalamus.[34,48] Control of cortical activity by the thalamus was first postulated by Berger.[5] Experimental evidence was offered by Dempsey and Morison[23] and later by Jasper and Droogleever-Fortuyn.[47] Hypothalamic effects on the cortex have been reviewed by Ingram et al. [46] and earlier by Murphy and Gellhorn.[69,70] The work of Magoun and associates has elaborated the role of brain stem structures in cortical activity. A further insight into the nature of this interdependence is given by the line of investigation started by Graham-Brown[38] who showed that the central nervous system was in a constant state of repetitive rhythmical activity.

In 1933, on the basis of extensive anatomical researches, Lorente de No[54] concluded that classic concepts of the reflex arc could not account for cells with short axons and recurrent fibers. He described many closed neuronal circuits and postulated them to be in constant activity, thus allowing efferent paths to be excited at various times.[55] He demonstrated this activity for the vestibular nuclei in particular, and a similar activity has been demonstrated for the phrenic motoneurons. [72] This concept was amplified by demonstration of the functional interrelations of the thalamus and sensory cortex and the inference that there was reverberating activity following excitation of either region.[68] Later work implied that the system did exhibit reinforcement from either cortex or thalamus, but that the thalamus alone could show repetitive activity. [48] This theory has met distinguished opposition,[7] but a recent experiment by Hsiang-Tung Chang[14] demonstrates that repetitive activity after a single sensory stimulus can normally be found in the cortex, or in the white matter, but in neither after cortical ablation. Indirect evidence for repetitive cerebral activity

From Department of Psychiatry and Neurology, Tulane University.

has been inferred from speech phenomena,[9] from studies on "after-discharge"[83] and from investigation of the alpha-rhythm, which, when driven by a photic flicker, will retain the imposed frequency for a brief time after cessation of the stimulus.[92]

The possible significance of this arrangement has been illuminated by the theoretical development of 'cybernetics' by Weiner et al.[94,100] While these concepts have not yet been widely validated experimentally, they have proven of value in explaining the nature of causalgia and of the tremor of cerebellar and basal ganglia disease. The theoretical development of this field will be of considerable heuristic value to neurophysiology (cf. 94).

Anatomy

For this discussion the cytoarchitectural map of Brodmann as modified by Walker will be used for reference, as this was the system used by most authors reviewed, as well as by the symposium on the frontal lobes published by the Association for Research in Nervous and Mental Disease.[78] The suggestion has been made that the system proposed by von Economo is more descriptive[78] (p. 84) but this has been protested by Mettler[65] who points out that no such scheme is wholly justified, but the Brodmann map serves as well as any.

In this section we shall describe both those connections traced histologically and those found by physiological neuronography.[25] The latter is not, strictly speaking, an anatomical technique, but since it sensitively shows functional connections, traces even unmyelinated pathways, and shows the normal direction of impulse propagation along the path, it is frequently a more informative technique than the classical methods of Marchi, Nissl, etc. The conclusions of this technique should eventually be demonstrated by refined histological techniques. The neuronographic results have been obtained mostly from experimental animals; the histological material from human brains following psychosurgical or other procedures.

For both man and monkey the prefrontal lobe of our discussion is that area rostral to the electrically excitable precentral motor cortex and the 'adversive eye field' (areas 4, 6, 8) and extends on the medial aspect of the hemisphere to the frontal end of the corpus callosum so as to include the precallosal portion of the cingulate gyrus. It can be divided into four divisions:[30]

I. The granular frontal cortex (areas 9, 10, 11, 12) best defined as the projection area of the dorsomedial nucleus of the thalamus (though it has other projections).

II. The orbital gyri (areas 13, 14), which project to the septum and possibly elsewhere.

III, The anterior cingulate gyrus (area 24) and the supracallosal gyrus (area 32) or limbic cortex, which projects to the anterior medial nucleus of the thalamus.

IV. Brocca's 'speech area,' (area 44, 45, 47) which region will be little mentioned. It has long been assumed that lesions in this area of the dominant hemisphere of man cause motor aphasia. This is impossible to evaluate in experimental animals, but in the Columbia Greystone series[65, p. 433] a patient with bilateral ablation of this area showed no loss of speech. Patients with removal of areas 45 and 46, however, showed significant though slight loss of verbal flexibility on the Capps Homograph Test.[65, p. 300] Suffice it to say that this region is probably not the definitive 'center' for speech function, and is probably important in the interrelations of the frontal areas. It presents a problem for further research.

The other three regions have important connections as follows:

Cortico-cortical—Intracortical connections are not as prominent here as are the long association tracts of other parts of the brain, although the cortical feltwork of fibers provides interconnection of all areas. The most readily identifiable tract is the uncinate fasciculus to area 38 at the tip of the temporal lobe, which contains fibers from area 13,[1] area 47,[71] and afferents to area 10.[78, p. 95]

Marchi studies after ablation of area 9 show connection with areas 6, 10, 12, 23, and particularly strong connections with 8 and 24.[64]

Neuronography shows projections from area 10 to area 32 and the contralateral area 10. (This is the only frontal area which has been found to have contralateral homocortical connections.)[2]

Area 11 has afferents from areas 21 and

22, but on strychninization shows only local activation.

Area 12 shows diffuse afferents to the opposite cortex and to the subcallosal gyrus.[2]

Area 14 has not been investigated well.

Area 24 has intimate two-way connections with areas 6, 8, 9, 10, 29[36] and 46.[62] It also has afferents to 4s, 6a, 31, and 32.[96]

Area 32 is interesting in that it receives afferents from each of the known suppressor areas of the cortex, but has no suppressor action itself and no efferents to those areas.[2] Its anatomy as well as its function remain obscure.

Cortex-Striatum—Ramon y Cajal[31, p. 328] described cortico-striatal connections consisting of unmyelinated collaterals from cortico-bulbar projection systems. These have been confirmed.[34] Mettler[64] finds that area 9 projects to the septal nuclei and the caudate via the subcallosal fasciculus. He suggests that caudate-cortex systems also exist.

Area 13 on strychninization activates both putamens, and the contralateral caudate.[82]

The main efferent connection of area 24 is that to the caudate.[32,34] (There are fibers to the caudate and globus pallidus from the centromedian nucleus of the thalamus, which in turn is thought to be an intrathalamic association center.)[31]

Cortex-Thalamus—McCulloch[58] has emphasized the importance of the thalamo-cortical projections and shown that the only reasonable classification of cortical regions is by thalamic projection areas. This has been reasserted for the frontal lobes in particular, and shown to give homologous relations for all mammals from rat to man.[78, p. 210]

The main afferent projection to areas 9, 10, 11, and 12 is that from the mass of dorsomedial nuclei of the thalamus.[17] These nuclei receive no connection from levels lower than the diencephalon, and serve as a cortico-diencephalic association center. A major function is the relaying of hypothalamic activity to the cortex. The tracts to and from the hypothalamus have been demonstrated anatomically[16] and neuronographically.[70]

It has been shown[28,66] that there is precise representation of the frontal areas in the thalamic nuclei. The antero-posterior of the nucleus projects on the same axis of the cortex.[64] For the dorsomedial nucleus (also referred to as the medial nucleus), the central part projects to the frontal pole, the lateral to the convexity, and the medial to the base. The pars magnocellularis (medial) projects to areas 11 and 12; the pars parvicellularis projects: the medial portion to areas 11 and 47, the dorsolateral to areas 45 and 46, and ventrolateral to area 8, and the central to areas 9, 10, and 6.[66] From area 9 efferents are traced to the "medial nucleus of the medial nuclear group, the reticular nucleus, the ventral nucleus of the ventral part of the lateral group, and the anterior nucleus of the ventral part of the lateral group of nuclei."[64] Other cortico-thalamic fibers have been described.[78, p. 278]

Areas 13 and 14 are as yet unidentified in the thalamus, but apparently they project to the septal nuclei.

Area 24 receives fibers from the dorsal part of the anterior nucleus; area 32 from the ventral.[78, p. 208] To the anterior nucleus projects the mammillothalamic tract of Vicq d'Azyr, which receives connections via the mammillary nuclei from the fornix system and hippocampus[17] and from area 6a.[97] Area 24 is the main projection area of the mammillary bodies, through the anterior thalamic nucleus. The projection from the hippocampus-fornix system may be an important association route from the temporal lobe and rhinencephalon to the cortical representation of the autonomic system.[56]

Cortex-Hypothalamus—Indirect relationships with the hypothalamus have already been emphasized.

Direct connections to the hypothalamus include a strong projection from area 6a both by Marchi[64] and strychnine studies.[97]

Areas 10, 46, and the 'orbital surface' (areas 13 and 14?) project to the paraventricular nuclei (which project to the neurohypophsis).[97]

"The frontal lobe anterior to the arcuate sulcus" projects to the supraoptic nuclei (and thence to the pituitary).[97]

Area 13 activates the median forebrain bundle, the H field of Forel and the lateral preoptic area on strychninization.[82]

Wall has described unmyelinated fibers from the orbital cortex direct to the anterior hypothalamic nuclei (supraoptic and

paraventricular) and to the ventromedial group.[31, p. 238]

Area 24 fires the "hypothalamus" on strychninization.[70] The mammillary nuclei project to area 23 and in turn to area 24.[78, p. 210]

Cortex-Brainstem and Cord—There are apparently efferents to the red nucleus,[67] to the reticular formation from area 24,[96] and to the pons via Arnold's bundle from the orbito-frontal cortex.[16] Beck[4] describes the prefronto-pontine bundle in man as arising from the dorsal and lateral prefrontal areas only and not from the orbital surface or frontal pole. These connections, though possibly important, are ill defined and will be omitted for the present.

Summary of Cerebral Organization

The frontal lobes have their major afferent connections from the hypothalamus via the dorsomedial nuclei of the thalamus for the orbitofrontal cortex, or the anterior nuclei for areas 24 and 32. The septal nuclei may also be important relay stations. In addition, direct corticohypothalamic connections have recently been found. (These connections suggest possible closed neural pathways (cortex-hypothalamus-thalamic nuclei-cortex).

Thalamocortical and perhaps cortico-thalamic paths are distinct for each area and suggest further such closed paths.

Strong connections of the dorsomedial nucleus with the lateral nuclear mass of the thalamus potentially provide for relation of the frontal cortex with motor and parietal areas. Relation with the temporal lobe is mediated via the uncinate fasciculus, and with the hippocampus via the fornix and mammillary nuclei to area 24.

Intracortical connections are particularly strong from area 24 to 32, and reciprocally between 24, 9, and 10. Intimate intracortical connection is provided by the cortical feltwork. Intra-hemispheral connections seem to be scant.

Physiologic Functions

That the hypothalamus has important actions on physiological functions is generally recognized. That the frontal lobes also have such actions is less appreciated, though descriptions of increased heart rate from frontal stimulation were made in 1875.[31, p. 468] Recent evidence comes from two types of experiments—stimulation and ablation. (N.B. Kaada[31, p. 464] reports that low frequency cingulate stimulation results in parasympathetic responses, while high frequency stimulation results in sympathetic responses, suggesting that the parameter of stimulation may be important.)

Motor—Ward reported stimulation of area 24 to cause marked loss of muscle tone (speculated to be via afferents to the bulbar reticular system), and abolition of corneal and deep tendon reflexes. Concurrently, there is suppression of the spontaneous electrical activity of the precentral motor cortex thought to be mediated via the caudate nucleus. Ward considers area 24 to be one of the major suppressor strips of the brain.[96]

A report of direct stimulation during craniotomy in man showed marked, reproducible, instantaneous motor quieting of an agitated patient.[83] The region was "superior 1 cm. and posterior 1 cm." to the tip of the corpus callosum.

Sloan and Jasper[85] object to the concept of area 24 as a suppressor area and equate its 'suppressor' action with "spreading depression." However, they report three types of immediate electrical changes in the cortex following stimulation by electrodes or by strychnine of area 24 ("electrically isolated"). These are: (1) Attenuation—i.e. decreased amplitude of burst activity with or without change in the pattern of activity. (2) Augmentation of bursts. (3) Activation or "arousal" responses either with increased or decreased voltage. They feel that this area may represent part of a system exerting regulatory effects on the whole cortex. (They also obtained from this area pupil dilatation, inhibition of G.I. tone and activity, and "changes" in B.P. and respiration.)

Ablation of area 9 or 6 bilaterally may cause monotonous, constant ambulation.[63]

Bilateral ablation of area 13 causes marked hypermotility of macaques.[22]

Autonomic Effects

Cardiovascular—Area 4 and 6 show hypertensive responses of 80-110 mm. of mercury systolic to weak stimulation.[43] Depressor points have also been found in the motor cortex.[11] Areas producing vasomotor changes show the same distribution as spe-

cific motor areas, so that stimulation of the arm area in a curarized subject results in vasodilatation of that arm only.

Stimulation of area 13 produces, with varying frequencies, both increases and decreases in systolic blood pressure. The anterior perforated space gives opposite effects on identical stimulation.[82]

Ablation of area 13 causes a marked elevation in the skin temperature of the extremities (i.e. vasodilitation)—contralateral, if unilateral ablation is performed.[22] It is interesting that Freeman & Watts[29] found marked drops of blood pressure in lobotomized, hypertensive patients still on the operating table. This was not found with the more discrete operations of the Columbia-Greystone series and may represent interference with orbital projection systems, or may be the result of shock, for Chapman et al.[15] found no effect on blood pressure following lobotomy. Stimulation of posterior orbital surface at operation however with 10 second stimuli of 10-30 cycles at 15 volts, caused consistent elevations of blood pressure which were small but statistically significant. Stimulation of area 24 anteriorly also causes a rise in blood pressure; posteriorly, a drop.[87] Posterior stimulation will further cause cardiac slowing and even arrest.[96] J. L. Pool also reports increased blood pressure on stimulation of "rostral cingulate gyrus."[73]

Hoff, et al.[43,44,45] report that stimulation of "the anterior sigmoid gyrus" in cats produces increased blood pressure and renal cortical ischemia. The latter is abolished by denervation of the kidney. In chronic experiments the kidneys gave the histological picture of "lower nephron nephrosis."

Respiration—Stimulation of area 13, or the anterior perforated space, will cause arrest in expiration.[82,15]

Stimulation of area 24 rostrally will cause respiratory slowing[96] or arrest[21] in lower animals, though only slight response was noted in man.[83]

Gastrointestinal—The exhaustive studies of Wolf and Wolff on emotional effects on gastric function have focused attention on possible cortical control. Cushing[19] described the gastrointestinal changes following intracranial stimulation. Strom et al.[91] report that discrete responses of various parts of the gastrointestinal tract could be elicited by stimulation of constant brain regions. From the anterior sigmoid gyrus and genual gyrus inhibition of motor activity was obtained. From the putamen and globus pallidus and the anterior olfactory tubercle, both augmentation and inhibition were noted. The tuberal and mammillary nuclei stimulated motor activity. They postulated that a cortico-subcortico-hypothalamic circuit controlled motor activity normally. Hesser et al.[42] reached similar conclusions by finding that increased gastric and esophageal tone and activity followed ablation of motor cortices.

Watts and Fulton[99] reported intussusception from cortical stimulation (particularly area 6). Davey[20] found increased gastrointestinal activity and intussusception following stimulation of area 8.

Stimulation of area 13 produces marked inhibition of gastric musculature.[3]

The Columbia-Greystone report[65, p. 153] suggests that lobotomy is followed by increased motility, while discrete ablation of area 6 causes decreased motility.

Davey et al.[21] finds that gastric secretion is stimulated by stimulation "just inside the upper curve of the arcuate sulcus" in monkeys and the most "anterior portion of the sigmoid gyrus" in dogs. He found increases in volume and pepsin in both dogs and monkeys and increased HC1 in dogs and unanesthetized monkeys. (He reported an optimum frequency of 50 cycles per second.)

The Columbia-Greystone Associates experiment suggested that ablation of area 9 caused a decrease in free acidity and ablation of 9, 10 or 11 caused a drop in total acidity,[65, p. 96] although the absolute values remained within normal limits. Review of the work by Carpenter[12] however, emphasized, "no alterations were found in excess of what is considered day to day fluctuation in the normal." Gastrointestinal hemorrhages are a common finding after lobotomy and lobectomy procedures.[78, p. 895, 31, p. 479]

Bilateral removal of area 44 has resulted in "remarkable diarrhea."[65, p. 96]

Other autonomic functions—Representation of sweating, micturition, piloerection, pupillary dilatation, lacrimation, and other

functions has also been demonstrated in the frontal cortex by stimulation procedures.[31, Ch. 23, p. 86]

Metabolic Effects

Sweet et al.[78] reported in detail the case of a physically well woman who, following bilateral frontal lobotomy, developed massive gastrointestinal hemorrhage; 11 days later, azotemia; 15 days later, hyperglycemia; 23 days later, hyperchloremia and hypernatremia. These symptoms became more severe until death resulted on the 32nd day from pulmonary embolism.

They also report on three similar cases with lesions in the neighborhood of the third ventricle and frontal lobes, and suggest that these cases may represent an interference with cortical connections to hypothalamic "electrolyte control centers." (These cases and those to follow may represent damage at subcortical levels but are included here for interest.)

A more carefully controlled series of six cases of uremic death following leucotomy has subsequently been reported.[60] Five of these patients had perfectly normal kidneys at autopsy; the sixth, chronic changes not suggestive of his acute uremic condition. In common, these cases showed injury of the posterior (agranular) quadrant of the orbital regions. Perhaps connections from area 47 to the head of the caudate were also severed. A further group of cases was reported who survived for about 11 weeks and then rapidly succumbed to "trophic deterioration" —marasmus, bed sores, sepsis, etc.—in spite of good nursing care and previous physical vigor. In these cases there was bilateral involvement of the subcallosal fasciculus at the level of the head of the caudate. The authors conclude that this tract, which connects the frontal cortex to the caudate, must be intact on at least one side to maintain life; and that the vital areas lie between the rostral part of the caudate and the cortex at levels of area 8 and 6.

Van Wagenen,[93] however, in his studies on the spread of epilepsy and on psychosurgical procedures reported a series of cases in which he sectioned the white fibers connecting cortex to caudate in this region without complication. None of his cases died, so there are no anatomical checks on his lesions.

Some control of glucose metabolism is suggested by the Columbia-Greystone Associates' finding that ablation of areas 9, 10, 24, 44, 45, and 47, alone or in combination, caused a significant rise in the glucose tolerance curve lasting two to three months, while ablating 6, 8, 11, and 46 did not.[65, p. 88] "Four weeks after bilateral frontal topectomy, patients showed a longer latent period between injections of insulin and minimal blood sugar levels than did normals. Five weeks after, a shorter time between subcutaneous epinephrine and maximal levels."[12]

Hemphill[41] reports the case of a 33-year old male who presented a severe obsessive neurosis and impotency of five years' duration. He had a small penis, small soft testicles, which on biopsy showed shrunken tubules, loss of seminal epithelium, and no mature sperm cells. He had little body hair, and his 24-hour excretion of 17-ketosteroids was 3.8 mg. After leucotomy was performed, and with no other therapy, his penis became larger; his testes firmer and larger with an enlarged scrotal sac. Four months later he had good libido and potency and later married successfully. His 17-ketosteroid excretion rose to 8.87 mg./24 h. The author felt that this dramatic change represented release of some cortico-pituitary inhibition.

An interesting, though perhaps not pertinent, case is that of an 18-year old boy who died with hyperthermia after lifelong signs of hypothalamic disturbance—chills, fever, oliguria, fluctuating blood pressure, episodes of asthma, somnolence, unconsciousness. He had underdeveloped genitalia and skeletal musculature. Careful histological examination revealed the only lesion to be in the right dorso-medial nucleus of the thalamus.[27]

Psychological Functions

The role of the frontal lobes in personality and intelligence is definite, but unindentified. It is of course difficult to accumulate a series of normal human individuals to be examined after ablation of frontal areas. Cases of trauma, neoplasm, etc. have formed the bulk of the material until the recent introduction of lobotomy, leucotomy, and topectomy for relief of pain. Observations in such cases are difficult to evaluate, for lesions are

seldom discrete and cause secondary effects by compression, irritation, etc. Further, evaluation of normal function from results obtained in psychotics is difficult for one is dealing with already impaired functions. However, recent, extensive psychological investigations of non-psychotic as well as psychotic patients following psychosurgery have been carried out. Experiments on other primates have been performed, and though not strictly comparable to findings in man, results have been given some insight into learning processes and the like.

The classic case of frontal lobe damage is that of Phineas Gage in 1848, who, after having a tamping iron blown through his frontal lobes, reversed his character to become quarrelsome, mischievous, lazy, and slovenly. The significance of his personality change was not recognized until years after the original report of his accident, though Wundt had already labelled the frontal lobes the center for "apperception," and before him Flourens had termed them the seat of volition. Workers since have attributed a host of functions to the frontal areas.

Among the reported results of frontal damage are "loss of attention," general excitement, loss of self-control, clownish behavior (Witzelsucht), impairment of association, loss of initiative, persistence of fear, memory defects, lack of ability to plan for the future, etc.[65] These findings are not universal nor related to type of damage, regions affected, nor are the results consistent from any individual to another. The extensive investigation of the Columbia-Greystone project failed to reveal any such consistent phenomena.[65, p. 488]

The psychologic investigations of frontal lobe defects have been numerous. The conclusions have differed radically from the contention that frontal loss has no marked effect on personality and intelligence[40] to the feeling that frontal lobotomy causes a patient to "lose his soul," and should be a procedure of desperation even in the psychotic.[78, p. 691] However, as data accumulates, a general picture emerges from two types of observation:

A. Animal (Mostly Simian) Experiment

1. Ablation or bilateral incision of area 14 leads to the "sham rage" syndrome, in which the animals seem wholly without fear and attack to kill.[31, p. 463]

2. Ablation of area 24[96] of the monkey causes it to lose its customary shyness and fear of man. It no longer shows mimetic activity nor the normal grooming or affectionate acts of monkeys. In cages with other monkeys the ablatees will walk over their neighbors, take their food, and generally behave asocially, evincing surprise when threatened with a fight and never fighting back. Ward described them as being "without social conscience."

3. Bilateral frontal lobotomy.[78, p. 3]

a. The most striking effect is the complete absence of frustration and rage reactions in chimpanzees following this operation. This observation, in fact, led Moniz to perform lobotomies on human psychotics.

b. The greatest deficit in behavior seems to be in the ability of the animal to maintain attention. This was reflected in learning and performance tests.

c. Harlow[78, p. 446] felt that he had separated this factor and found in addition a specific decrease in learning ability.

d. Stanley and Jaynes[89] have done an analysis of the behavioral defects appearing in simians after lobotomy. Briefly, they suggested that the essential difference in tests which the animal performed poorly and those he performed successfully was the necessity for inhibiting a response pattern in the former.—e.g. Distinguishing between noxious and pleasant stimuli in a learning problem is done effectively, but inhibiting the response to one of two similar immediate stimuli in the delayed response problem is not done well. They applied this concept to the eight types of behavioral change generally observed and postulated a "cortical act-inhibition" which was impaired following lobotomy. These experimentors also point out that the behavioral "silence" of the frontal areas on stimulation may be due to the fact that the animal is not stimulated *while behaving.*

4. Working on learning processes in the rat, it was concluded that *symbolic processes* in the rat were subserved by the frontal projections of the dorsomedial nuclei, roughly

homologous to areas 9, 10, and 12 in the primate.[90]

B. Human Experiments

1. Personality—A resume[65, p. 481] of the defects following lobotomy (in psychotics) includes "slight impairment in ability to generalize, a tendency to perseverate, euphoria, apathy, procrastination, facetiousness, temper outbursts and distractability, impaired judgement, lack of planning for the future, and loss of creative imagination."

In the Columbia-Greystone series of purely cortical ablations (also in psychotics) the only definite permanent effects in this sphere were increased distractability and greater sensibility to external stimuli.[65, p. 487]

The factor of distractibility has been consistently noted in such cases and has been tested by measuring pain thresholds of individuals concentrating on a problem. It is found that lobotomized patients have lower thresholds than normals.[57, 78, p. 754] One worker concludes that the lobotomized patient has "lost the ability to maintain a mental set in the face of adversity." This finding is reminiscent of the hypothesis of impaired cortical act-inhibition, and may represent the same phenomenon.

2. Intelligence—The extensive psychological examinations of the Columbia-Greystone Associates revealed only transient deficits in intelligence and learning ability as usually tested, centered in the main around inabilities to generalize and form abstract concepts. These test impairments were not found after three months and those psychotics who showed improvement in other spheres usually showed improvement in test scores.

The examination of non-psychotic subjects would seem to yield more valuable information. Studies on such subjects after lobotomy[78, p. 723, 8] have consistently found impaired intelligence, particularly in the ability to abstract and form generalizations. It may be that this loss is not marked after lobotomy in schizophrenics, the most commonly operated group, because this impairment is a basic one in schizophrenia. While most investigators have not found clear-cut impairment of a specific function, Halstead[39] feels that his tests demonstrate four separate, basic factors of intelligence. One of these, "A" the capacity for abstracting universals or forming rational concepts, he believes to be maximized in the frontal lobes, although a general property of cerebral cortex, and to be specifically impaired by lobotomy.

Russell[81] has suggested that the frontal lobes are most important in children while learning, whereas adults have stereotyped their learning and more subtle changes occur. In support of this thesis, he has shown that frontal lobe injuries in otherwise normal children produce far greater intelligence deficits than those reported for adults.

3. Flicker Frequency—An interesting finding, as yet not correlated, is the Columbia-Greystone observation[65, p. 311] that there was a significant lowering of the "Critical Flicker Frequency" of 7 of the improved patients and 2 of the unimproved. This may have no bearing on frontal lobe function, but it is of interest to note that cerain flicker frequencies will produce marked *affective* responses in normal individuals.[95] (Other fascinating work on flicker frequencies and related phenomena is found in Stroud's discussion at the Cybernetics Conference.)[94]

More definite than the changes in normal function are the effects of cortical ablation on two pathological states, pain and anxiety.

4. Pain—Some patients with intractable organic pain respond remarkably both to lobotomy[78, p. 706] and to topectomy (removal of areas 9, 10, and 46.)[51] The patient reports that pain is still experienced but that he no longer reacts to his suffering; the pain has become "a sensation rather than a threat."[78, p. 715] Frequently the postoperative patient will describe his pain in the same terms as before operation but he will no longer be bedridden nor need narcotics. Apparently a vicious circle of fear and mental pain reinforcing the sensation of organic pain has been broken. Removal of only area 9, 10, and 46 will produce this effect, and with less damage to personality than a lobotomy.[51]

5. Anxiety—The most impressive results of psychosurgical procedures are produced on the psychotic or severely neurotic personality. Solomon[88] reports the following personality changes after operation:

"1. Tension, apprehension, fear, worry, and agitation are greatly reduced or abolished.

2. Excitement, aggressive and assaultive behavior, emotional outbursts and rage-like exhibitions, although not infrequent shortly after operation, tend to diminish . . .

3. Paranoid ideas tend to lessen to the vanishing point, or . . . cease to lead to overt expressions.

4. Obsessive thinking becomes less distracting, compulsive actions no longer occur, and ritualistic behavior ceases.

5. Long standing hallucinations may lessen . . ."

With topectomy, these desirable results may be achieved without the blunting of emotions, etc. described earlier.[65,74]

The consistent psychological finding in the Columbia-Greystone Association series was marked diminution of the "Anxiety and Complaint" scores in patients with areas 9, 10, and 46 removed. Some improvement was noted even in those patients who failed to make good recoveries.

The reasons for this reduction of tension and anxiety, and alleviation of psychotic manifestations are disputed. After comparing other theories with the Columbia-Greystone Association results, Heath et al.[65] conclude that lessening of the painful affect associated with certain memories is the basic factor at work. They note[65, p. 418] that "all patients in whom improvement was related to operation had at least part of area 9 or 10 removed. Those who remained well had the junction of areas 9 and 10 included in the removal, whereas temporarily improved patients had only partial removal of other regions in 9 or 10." (The latter conclusion has been criticized.)[6]

LeBeau[51] also concludes that areas 9, 10, and 46 "may have some specific relation to anxiety."

There may be significance in this respect to the report of six psychotics who had relapsed (and eventually died) after initially successful leucotomy, in whom the only constant anatomical finding was preservation of area 9 and the gyrus rectus.[61]

Summary

Ablation or isolation of frontal cortex in non-psychotic individuals and lower primates causes a decrease in "intelligence."

This is partly due to an increased distractibility (perhaps a deficit in "cortical act inhibition") and partly to an impairment of "abstract thought."

Removal of orbital areas causes hypermotility and rage reactions in monkeys. Removal of large amounts of cortex results in a deterioration of social behavior and blunting of emotions in man and animal.

Intractable organic pain and neurotic and psychotic tension states are often relieved by either severance of the whole frontal lobe, by lobotomy, or by topectomy.

The latter procedure, removing on 9, 10, and 46, seems to be the one most free of undesirable effects and to specifically diminish emotional tension.

Comment: Throughout this review it has been simpler to separate and classify functions as well as anatomic areas. It is worth reemphasizing that things are not so simple *in vivo*. The areas where our knowledge is most scant are the borderlands between psychology and physiology, psychology and anatomy. We must eventually abolish such dichotomies from our thinking and research if we are to progress.

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An Arctic Survival Ration: Psychiatric Observations

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This is a report on one phase of a series of studies by the Arctic Aeromedical Laboratory on Arctic survival. The main purpose was to ascertain the physiological effects of the diet, but it was also deemed desirable to estimate the emotional factors involved.

For ten days the subjects subsisted on 1000 calories per man per day (4 men ate only protein; 5 only carbohydrate; and 2 half protein and half carbohydrate), with unlimited, but recorded, amounts of water. The test took place in winter in the Arctic; the men slept in tents, and were required to travel at least ten miles per day by foot, skis, or snowshoes. The range of temperature during the experiment was minus thirty-six degrees Fahrenheit to plus twelve degrees Fahrenheit, and the mean temperature was minus fifteen degrees Fahrenheit.

Eleven volunteers from an infantry company were chosen to participate in this experiment. All of these men had been in Alaska from seventeen to twenty months, had been well trained in Arctic survival, and were in good physical condition. The edu-

cation of the men was from the sixth to the twelfth grade, two having completed high school and all of the others except two having completed grammar school. The family background of eight men was judged to be good to excellent and that of the remaining three was judged to be poor to insecure. Of these three, one had been abandoned by his parents in infancy; another came from a home broken by divorce and the mother of the third died from tuberculosis when he was an infant.

There were three main reasons for the soldiers' volunteering. They wanted the furlough which was promised on successful completion of the experiment; they were bored with routine military life; and they were interested in the project to the extent that they wanted to see if they were able to take the hardships. None of the soldiers were serious offenders, but six members of the group had suffered military punishments for petty offenses, such as being AWOL, drunk and disorderly. All were thoroughly screened from a psychiatric standpoint before the project started, and none of them could be diagnosed as having an actual or latent psychosis, psychoneurosis, or character disorder. Three men were classified as immature personalities and two were above average in maturity and reliability. Of these two, one was a sergeant first class and the other a sergeant. They were selected as group leaders.

From the beginning of the experiment, it was recognized by the subjects and the investigators that several factors of emotional importance were excluded. The soldiers were in good health and well clothed. They had contact with the outside world through their observers, by going to the Company area to wash and collect mail three times during the project, and by being at all times on the military reservation. They were not lost and they knew that the project would last only ten days. Almost all sources of anxiety and fear were therefore removed, and whatever the emotional difficulties would arise could be attributed to the diet, the inconveniences of camping out, the cold, and personality maladjustments. The cold as a promoter of fear and anxiety had very little influence since the men were accustomed to cold weather and had many times been on field maneuvers in temperatures sixty to eighty degrees below freezing.

Both by observation and by interview with the men after the completion of the experiment, the following observations were made:

1. There was an increase in carelessness. The soldiers had all been thoroughly indoctrinated in taking care of themselves and of their equipment in the Arctic and it was expected that they would continue to show the results of this training. On one occasion a fire was started in one of the tents; and several of the soldiers burned their socks and shoes. The men stated that they noticed no increase in carelessness, but the observers and the sergeant in charge of the group did notice increasing carelessness.

2. Five of the men felt increased desire to sleep and they slept from one to six hours more than usual. Reasons given for this were that there was not enough to do, that they went to sleep to keep warm, that they were tired from the exercise and low energy diet.

3. The leaders of the group noticed that most of the men were more irritable and inclined to quarrel, especially on the last two days of the experiment. Two of the men admitted that they found themselves more irritable, but the others saw no change in themselves or in their fellows.

4. All of the men stated that they had less energy on each succeeding day of the experiment and the group leader observed that the men were slower to respond in obeying orders.

5. Six men reported occasional dizzy spells on postural changes and during exercise. Three of these were on protein diet, two on carbohydrate, and one on the combination of protein and carbohydrate. Two men on protein diet had sharp abdominal pains during exercise and one man on combination diet had moderate cramps in the calf muscles on exercise.

6. All of the group thought more of food than usual and were inclined to talk about food much more frequently. However, some of them would leave the group when the conversation turned to food. Five men had dreams of food.

7. There was no increase nor decrease in sex thoughts and fantasies.

8. Two men on the protein diet noticed increased thirst, three noticed increased hunger. Of those on carbohydrate diet alone, two found increased thirst, and four increased hunger. Of those on combination diet, there was no increase in thirst, but two found increased hunger. From the low calorie content of the diet increased hunger was expected, yet some of the men on protein diet did not eat all of their ration because it was unpalatable.

9. The entire group gained increased confidence to withstand physical hardships. Before the beginning of the experiment, all but two felt that they would not be able to last the entire ten days. At the close of the experiment, all of the men felt that they could have continued on for five to ten days longer.

Summary:

1. In a ten day ration survival test no major personality changes were noted. There was an increase in carelessness, irritability and desire to sleep. There was a decrease in energy. All of the men finished the test with more confidence in their own resources.

2. There were mild symptoms of cramping, abdominal pains, and dizziness which could not be definitely ascribed to either a functional or organic cause.

3. Increased hunger was expected and noted. There was also some increased thirst. The protein diet was unpalatable to the majority of the men.

4. There was no significant deterioration in morale, and it is the opinion of this observer that at the end of the project the soldiers were in condition for combat.

Narcosynthesis Effects of Sodium Amytal, Methedrine and L. S. D-25

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L.S.D-25, a derivative of ergot, is a d-lysergic-acid-diethylamide, a synthetically manufactured amide of the organic d-lysergic acid with a secondary amine, diethylamine. As it is difficult to dissolve in water, it is used in the form of soluble tartrate. In the original publication by W. A. Stoll, the drug was termed "A phantasticum of the ergot group." The reason for this somewhat eccentric name, may be found in the effects which accidental inhalation of the drug had on the chemist, Dr. Hoffman. This is his description: "In the middle of the afternoon, I had to interrupt my work in the laboratory and return home as I had been overcome by a slight dizziness. At home, I went to bed and sank into a not unpleasant state of intoxication which manifested itself in an extremely stimulated phantasy activity. In this twilight state, with my eyes closed (I perceived the daylight as unpleasantly glaring), fantastic images with a marked relief quality and with an intensive kaleidoscopic play of colors, acted upon me. After approximately two hours, this state passed." (W. A. Stole: Lysergsäure-diäthylamid, ein Phantastikum aus der Mutterkorngruppe. Schweizer Archiv für Neurologie und Psychiatrie, Band LX, 1947.) Having some doubt that he could have inhaled a sufficient amount to cause those reactions, Dr. Hoffman took 250 Y of d-L.S.D. in a watery solution. This self-experiment produced effects similar to those just described. On the basis of this report, the drug appeared promising as a possible aid in narcosynthesis.

Methedrine, commonly known as Pervitin, is a d-n-dimethyl phenethylamine hydrochloride. As a potent stimulant of the central nervous system, according to studies in different places, including our own, this drug, too, seemed likely to contribute to methods of narcosynthesis.

From Saint Elizabeth's Hospital, Washington, D.C.
This report was presented at the Regional Research Association Meetings under the auspices of the A.P.A., University of Virginia, Charlottesville, April, 1952.

The well known narcosynthesis effects of Sodium Amytal were tested on our patients for the purpose of obtaining data under conditions as similar as possible and therefore reasonably valid for comparison.

The three drugs were used in the same 20 cases with the following diagnoses: Manic Depressive Reaction, Manic Type, 1; Schizophrenic Reaction, Catatonic Type, 8; Schizophrenic Reaction, Catatonic and Paranoid Tyes, 2; Schizophrenic Reaction, Paranoid Type, 1; Schizophrenic Reaction, Hebephrenic Type, 3; Schizophrenic Reaction, Catatonic and Hebephrenic Types, 1; Schizophrenic Reaction, Chronic Undifferentiated Type, 1; Involutional Psychotic Reaction, 1; Psychoneurotic Reaction, Mixed Type, 2. Out of fifteen schizophrenic patients, 8 were completely mute; 7 would not talk spontaneously and would answer questions only with "yes" or "no," "I don't know," "I forgot."

Procedure:

Any significant abnormalities in the physical or laboratory examinations were regarded as contraindications. Immediately before the administration of any of the drugs, the following physiological and psychological reactions were noted: Color of the skin, pupils, reflexes, spontaneous personality reactions and those evoked in short interviews.

Dosage: Methedrine was administered intravenously, from 5 to 20 mgm; 10 to 15 mgm seemed to be most effective. The drug was administered 2 or 3 times, at intervals of 3-5 days or longer. In order to facilitate the intravenous administration of the drug in the appropriate dosage, we diluted the 1 cc ampule, containing 20 mgm of the drug, with 3 cc of distilled sterilized water, used for i.v. injections.

The physiological and personality reactions, spontaneous reactions and those obtained in interviews, were noted for one hour following the injection.

Sodium Amytal, in accordance with the usual procedure, was given intravenously from 0.3 to 0.5 gm. in each patient once. The patient's reactions, both physiological and psychological, were observed during and one hour after the injection.

L.S.D-25 is furnished in 1 cc ampules, each ampule containing 0.1 mgm (0.0001 gm) of the active substance. The contents of the ampule was diluted with 9 cc of distilled water to comprise an oral solution, 1 cc of which contains 0.01 mgm (0.00001 gm. or 10 gamma). The oral solution should be made and stored in a dark glass bottle; it should not be used beyond the third day after preparation. The dosage, given orally varied from 1 cc to 5 cc (10 to 50 gamma); 2.5 to 4.5 cc (25 to 45 gamma) appeared to be most effective. The patient's physiological and personality reactions, again spontaneous ones, and those elicited in interviews, were noted within two or three hours after administration of the drug.

TABLE 1:

Physiological Reactions in 20 Schizophrenic Patients

	Color of Skin	*Pupils*	*Knee Reflexes*	*Pulse*	*Respiration*	*Blood Pressure*
METHEDRINE:	Flushing or Mildly cyanotic	Dilated	More active	Increased up to 28	Normal or increased	Raised 20-50 mm
SODIUM AMYTAL:	normal or flushing or mildly cyanotic	normal or contracted or slightly dilated	less active	usually decreased; increased with strong emotional reactions	no change	lowered 12-40 mm
L.S.D-25:	flushing pale in 2 patients	dilated	more active	increased 8-32	usually increased	raised 22-50 mm

TABLE 2:

Emotional Reactions Following Administration of the Drugs to the Same 20 Patients

	Methedrine	*Sodium Amytal*	*L.S.D-25*
1—Inappropriate giggling, laughing or euphoria:	5	4	9
2—Negativistic, hostile or threatening:	2	3	1
3—Relaxed, pleased, or friendly:	7	5	3
4—Depressed, tearful, sighing or weeping:	4	2	6
5—Dazed, preoccupied, or drowsy:	2	6	1
Total	20	20	20

TABLE 3:

Talking Spontaneously or in Answering Questions Following Administration of the Drugs to Same 20 Patients

	Mute Patients—9		*Relatively Mute Patients—6*		*Average or Above—4 Average Talking:*		*Reticent to Talk—1*
SODIUM AMYTAL:	Adequate	7	Adequate	5	No significant change	2	
	Mild	1			Increase	1	
	Remained mute	1	Remained mute	1	Decrease	1	
					(Hypertalkative before drug)		Increase
METHEDRINE:	Adequate	5	Adequate	6	No significant change	3	
	Mild	1			Increase	1	Increase
	Remained mute	3					
L.S.D-25:	Adequate	4	Adequate	3	No significant change	2	
	Mild	1			Increase	1	
					Decrease	1	
	Remained mute	4	Remained mute	3	(Hypertalkative before drug)		Increase

Discussion

TABLE 1 summarizes the physiological reactions.

These reactions indicate that the three drugs affect both the autonomic and the cerebrospinal nervous system. Methedrine and L.S.D. provoke predominantly sympatheticotonic reactions. The sedative effect of Sodium Amytal appears to manifest itself on the physiological level in a relative parasympatheticotonia and in diminution of the reactivity of the cerebrospinal nervous system.

The psychological reactions, subdivided into emotional reactions, spontaneous verbal production and that obtained in interviews, are as follows: Emotional ventilation (Table 2) was provoked by either of the three drugs; it was most marked with L.S.D.; less with Methedrine, and still less with Sodium Amytal. Verbal production, (Table 3) spontaneous and in response to questions, increased in 14 cases and did not change in 6 cases with Methedrine; it increased in 15 cases, decreased in 1 and did not change in 4 with Sodium Amytal; it increased in 10 cases, decreased in 1 and did not change in 9 with L.S.D.

The three drugs failed to provoke verbalization in one and the same mute patient who showed intense ventilation of emotions (laughing, giggling, gesturing).

We found a consistent relationship between verbal production and changes in the blood pressure; with Methedrine and L.S.D., increased verbalization was associated with increased systolic blood pressure, from 20 to 50 mgm of mercury; with Sodium Amytal, increased verbal production was associated with fall in the systolic blood pressure, from 20 to 40 mgm of mercury.

The general content of the patients conversations consisted of: delusions or auditory hallucinations of being accused and, therefore, feeling guilty, deserving punishment or being punished; successes and disappointments in love affairs; sexual experiences and fantasies; domestic difficulties; experiences in the military service; general information to a considerable extent. The experiences included more or less remote happenings,

genuine, or more or less distorted or entirely delusional happenings. The content varied in different patients and in the same patients at different times of testing, but, apparently it did not depend significantly on the kind of the drug administered.

Advantages and Disadvantages of the Drugs
Sodium Amytal:

Advantages: 1—Because of its sedative effect, it is the drug of choice in uncooperative or excited patients. 2—Since it reduces blood pressure, it is most appropriate in patients with high blood pressure. 3—Like the other two drugs, it provokes marked ventilation of emotions.

Disadvantages: 1—Not infrequently the twilight state cannot be maintained: the patient may fall asleep too rapidly. Its effect may, therefore, be of too short a duration for obtaining sufficient material. 3—The patient may recall relatively little of the elicited material.

Methedrine:

Advantages: 1—The effect of the drug lasts for several hours and the patient remains awake. 2—There is, therefore, greater opportunity for the patient to ventilate his emotions and to bring forward material, either spontaneously or in the interviews. 3—The patient usually feels better. The performance, therefore, is apt to contribute favorably to doctor-patient relationship.

Disadvantages: 1—Because of its effect on the blood pressure, it is preferable not to use it in patients with hypertension. 2—A minor disadvantage is that its administration should be limited to the forenoon hours; otherwise, it may disturb the patient's night sleep.

Possible Untoward Effects: Headaches 2 cases; precordial discomfort 1 case; dizziness 1.

L.S.D-25:

Advantages: 1—The drug has no odor and no taste; its oral administration is, of course, the easiest. 2—The stimulating effect of the drug makes the patient feel better. 3—The effects of the drug are of longer duration than with Sodium Amytal. 4—When the effects of the drug wear off, the patient recalls what he said while he was under its influence.

Disadvantages: 1—If the patient is uncooperative, it is impossible to administer the drug, as it is given orally. 2—It is contraindicated in hypertension. 3—The test has to be repeated several times because the individual sensitivity towards the drug varies. One, therefore, begins with a small dose; according to the patient's reactions the dose is increased at successive tests until the optimum dose is reached, without provoking severe physiological reactions.

Possible Untoward Effects: Abdominal discomfort in 3 cases; tremor in 2 cases; ataxia in 1 case.

Summary and Comment:

Sodium Amytal, Methedrine and L.S.D-25, studied in the same 20 patients and under the same conditions, have proven their effectiveness in narcosynthesis.

The physiological reactions of Methedrine and L.S.D-25 are similar and preponderately sympatheticotonic. Those of Sodium Amytal are predominantly parasympatheticotonic.

Ventilation of emotions appears to be more marked with L.S.D. than with either Methedrine or Sodium Amytal. Since the effects of Methedrine and L.S.D-25 last considerably longer than those of Sodium Amytal, there is greater opportunity for the patient's ventilation of emotions and for verbal production.

Because of the hypertensive effects of Methedrine and L.S.D-25, and the rather hypotensive effect of Sodium Amytal, the latter drug is to be preferred in patients with high blood pressure.

The method of administering L.S.D-25, namely, by mouth, makes this drug eminently valuable in most patients who would rather not subject themselves to intravenous injections.

Each of the drugs offers advantages and has disadvantages sufficiently marked to determine the preference of drug to be used on a given patient under specific conditions.

Neurological Clinical Pathological Conference

of the
Cincinnati General Hospital
CHARLES D. ARING, M.D., *Editor*
CASE NO. 275696

Presentation

A 76-year-old single white woman entered the hospital for the second time July 11, 1951 at 4:30 A.M., complaining of dyspnea. She expired 6 days later.

History: The patient was never able to give a complete history. For two years she had suffered from a swollen right leg for which she had worn a bandage. She also stated that she had heart trouble but further details of symptoms or treatment were not elicited.

She first came to the Surgical Service of the hospital June 13, 1951, complaining of incontinence of urine and inability to eat for 24 hours. Temperature was 102° F. She was obese. The heart was normal but fine moist rales were heard over the bases. Her pulse rate was 84, respirations 26, and blood pressure 130/70. Bilateral ankle edema was more severe on the right and there was redness and increased heat of the right lower leg.

Hemoglobin was 14 gm. per cent and the white cell count 4,600 per cmm. The urine was loaded with white cells and gave a 2 plus test for albumin. Urine culture yielded E. coli. Blood urea nitrogen was 20 mg. per cent. A Kahn test of the blood was negative. An electrocardiogram was normal. A chest film showed minimal cardiac enlargement and possibly some pulmonary congestion.

She was given penicillin and gantrisin. A medical consultant found slightly distended neck veins, 2 plus pretibial edema and basal rales. Digitalis was ordered. Although she remained lethargic, temperature fell to normal on the fifth day and the inflammation in the leg subsided. She was discharged June 21, 1951.

She was seen July 9 in the Cardiac Clinic where basal rales were heard and the continued swelling of the right foot and leg observed. On the way home from the clinic she had shortness of breath and abdominal pain. Medication given by a physician was followed by several bowel movements and transient relief of pain. With continued dyspnea, abdominal pain and later back pain, she returned to the hospital July 11.

Physical Examination: Temperature was 100°. She was acutely ill with dyspnea and mild cyanosis. Neck veins were not distended. Bilateral basal rales were heard. Respirations were 30. The heart was not enlarged and the rhythm was regular. No murmurs were heard. The aortic second sound was louder than the pulmonic. Pulse was 104. Blood pressure in the left arm was 160/95. The right arm was cooler than the left and no pulse was found in the radial and brachial areas but axillary pulsations were palpable. The right femoral pulse was weaker than the left and no pulse was found in either foot. Both legs and feet were swollen; the right was nearly twice the size of the left. Homan's sign was elicited in both legs. The obese abdomen showed no spasm or tenderness and no masses were felt. Normal peristaltic sounds were heard. Neurological examination was normal.

Laboratory Data: Red cells of the blood numbered 4.3 million and the hemoglobin was 12 gm. per cent. The white cell count was 12,600 with 85 per cent neutrophils on admission and 19,200 the following day. The sedimentation rate was 35 mm. per hour. A sample of urine obtained by catheter on admission showed: specific gravity 1.025; negative tests for sugar and albumin; occasional red and white cells in the sediment. On the following day a catheterized specimen showed 2 plus albumin and the sediment was loaded with white cells. The specimen of July 13 was similar but also contained 100 red cells per high power field. Culture yielded aerobacter aerogenes. A Kahn test of the blood was negative. Blood urea nitrogen was 16 mg. per cent on admission, rising to 110 mg. per cent the day before death. Values for carbon dioxide combining power remained around 20 meq. per liter and chlorides between 95 and 100 meq. per liter. Serum bilirubin was 0.4/1.1 mg. per cent but a liver profile was otherwise normal. Two blood cultures yielded no growth. On July 13 lumbar puncture yielded clear fluid with initial pressure of 160 mm. of water. Two white cells per cubic millimeter were found. Protein was 43 mg. per cent, glucose 121 mg. per cent and chlorides 125 meq. per liter.

Roentgen Findings: Postero-anterior teleo chest film showed the transverse cardiac diameter at the upper limits of normal size. There were increased markings bilaterally in both lung fields but no evidence of fluid was seen. The left lung appeared more radiolucent than the right, but this was attributed to rotation.

Electrocardiographic Findings: Three electrocardiograms were similar, showing sinus tachycardia, Q wave in Lead III and AVF, and ST depression in leads over the left ventricle. Diagnosis was abnormal record with possible previous posterolateral infarction.

Course in the Hospital: She was treated with oxygen and sedatives. Heparin and dicumarol were also given but discontinued after two days when the prothrombin concentration fell to 10 per cent. At 10 A.M. on July 11 she had a clonic seizure involving the left side of the body with turning of the head to the left, which lasted for 8 minutes and was treated with sodium amytal intravenously. She awoke at noon complaining of epigastric pain. Left

sided weakness with flaccidity of the left arm was found. At 3 P.M. no pulse was found in the left arm. Femoral pulses were equal. The abdominal pain persisted. On the following day, July 12, the left axillary pulse returned. The abdomen became distended but she did not complain of pain. Blood pressure in the left leg was 240/160 and she had fever to 104°. Penicillin treatment was instituted. Bright red urine appeared July 13 and guaiac positive stools were found. A sharp apical systolic murmur appeared. She responded poorly throughout the day. Both legs and the left arm were flaccid. No other neurologic phenomena were recorded. The temperature rose to 105°. Aureomycin therapy was started and the dosage of penicillin increased from 300,000 units to 1,800,000 units daily. Slight percussion dullness and tubular breathing were found over the right base. Gallop rhythm appeared on July 14. She remained in poor condition for the next two days. Temperature reached 104°, pulse 115, and the respiratory rate was around 45. There was another convulsion in the evening of July 16 and fever reached 109°. On the following day she was very dyspneic and became cyanotic. Loud rales were heard throughout the lungs and mucus was aspirated from the throat frequently. She expired at noon on July 17, 1951.

Differential Diagnosis

*Dr. Eugene A. Stead, Jr.**: This case presents the problem of a 76 year old lady who had been ill for two years. The historical data on admission is not complete and we cannot build many premises upon it. All we have to figure out then is a disease which will kill in approximately 4 weeks from the first time that the patient was received in the hospital. This disease must involve the blood vessels because the most striking thing in reading over the protocol is that at various times blood vessels were obstructed. She lost pulses here and there which occasionally would return but by and large the rate of loss was greater than the rate of recovery. This process, whatever it is, seems to obstruct blood vessels because in due time we find not only involvement of the veins but also of the arteries.

We know from her history that she had thrombophlebitis of some type over a period of two years before she came to the hospital. This immediately raises the question whether she could have been having embolic phenomena to her lungs and the development of signs of cardiac insufficiency and dyspnea on the basis of the progressive stopping up of her lungs. Against the explanation that the venous thrombosis is the primary illness is the fact that as the illness developed everything seemed to get over on the arterial side. She began to have more and more arterial occlusions and in the absence of a right-left shunt it is difficult to make the pathology primarily venous. I am inclined to believe that the old thrombophlebitis which may or may not be demonstrated, depending upon the extent of the postmortem examination, is not important in this particular illness.

Then we come to the question of whether anything could have happened in the aorta to occlude the blood vessels coming off it. In a dissecting aneurysm, the vessels coming off the aorta may be occluded. Indeed, we suspect dissecting aneurysm primarily when the following combination of events occur. The patient has an acute and sudden pain in the chest. This pain, if it begins anteriorly in the chest, frequently migrates to the back and on down into the abdomen. Associated with this we find enlargement of the aorta which we can feel in the abdomen or see by x-ray, or there occur occlusive phenomena in the vessels coming off the aorta. If we examine the sequence of vascular signs in our patient, I think the evidence is against there being occlusive phenomena as the result of dissecting aneurysm. If that had been the case the occlusions would have been at the origin of the vessels from the aorta. She had palpable axillary pulsation on both sides after she had lost the brachial and radial pulses on one side. I would have thought that as far as we could tell from the way this occlusive disease occurred, that it is not that characteristically seen in people who have dissecting aneurysms. It is of interest that hemiplegia is not uncommon in the picture of dissecting aneurysm. Sometimes it occurs on an obvious basis from occlusion of the carotid artery and at others somewhat more mysteriously and we are unable to tie it in morphologically with actual obstruction of a vessel from the dissection itself. I think I am willing to say she did not have a dissecting aneurysm.

Then we come to the question of whether or not we are dealing with myocardial infarction. As you know, people who have

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myocardial infarction can have mural thrombi, and people who have mural thrombi can have emboli, and these emboli can go to any and all places. We know that electrocardiographic changes occurred between the time she was first seen and the time of her second admission. The first electrocardiogram was described as normal and the second electrocardiogram as possibly indicating a posterior lateral infarct. We can only say that this patient did not present a characteristic picture of myocardial infarction. She did not have the expected type of pain. She did not, as far as we know, have hypertension or any other symptoms pointing to generalized arteriosclerotic vascular disease.

Idiopathic myocarditis, occurring with or without varying degrees of degeneration and infiltration into the muscle of the heart itself, associated with cardiac dilatation and enlargement, frequent arrhythmias, and conduction defects, has a high incidence of embolic phenomena. Pulmonary infarctions are common in this syndrome. So we would say that a non-specific, etiologically undetermined myocarditis with embolic phenomena present on the basis of mural thrombi would be an entirely acceptable diagnosis. I think, that is a distinct possibility but I admit that I do not have much enthusiasm for it, but I cannot eliminate it.

We are in an era when people always get drugs and this patient was given gantrisin and penicillin. We have to face the possibility that these drugs might have set off an arteritis which might have been associated with thromboses. We might say that she was akin to one of Dr. Rich's rabbits. She received gantrisin and penicillin, drugs which could have produced a progressive, widespread blood vessel disease. All we can say about this is that this remains in the realm of possibility.

Because of our responsibility as physicians I think we must ask another question. Is there any disease that this woman had for which she might have been treated? I confess I cannot think of any of the commoner situations in which therapy would have been helpful. The only myocarditis that I can recall that is capable of causing the widespread occlusive phenomena and of killing in roughly the fourth week of illness, and in which therapy might be important, is concerned with parasites. Now I can never remember much about worms and, therefore, I always have to do some research to see if there were any kind of worms which might be responsible. Since the patient could not give any adequate history, it is likely that we do not know exatly what happened when she first became ill; then the picture is perfectly compatible with worms. If pork containing Trichinae is consumed, a picture similar to the one seen here is occasionally produced. We should have a story of the acute invasion with fever, muscle pain, swelling of the eyes, hemorrhages under the nail beds, leucocytosis and eosinophilia. We do not have this historical data. In a few instances the passage of larvae through the brain, heart and lungs results in local tissue sensitization sufficient to cause a violent reaction in these organs. When the patient is seen in the fourth week of the illness, one is impressed by the signs of myocarditis, with pulmonary and peripheral embolization and involvement of the nervous system. In this stage, eosinophilia is not so pronounced and may be absent. The signs of heart failure, vessel occlusion and neurological phenomena dominate the picture. Preliminary reports have indicated that ACTH may be effective in treatment.

In conclusion, I think that we have a disease capable of occluding arteries and veins. Dissecting aneurysm and bacterial endocarditis do not fit the picture. The clinical picture in the absence of a really good history is perfectly compatible with trichinosis and as that is now a treatable state I would place it as my first choice. In second place I would list a diffuse non-specific myocarditis with embolic phenomena. Third, I would list the possibility of coronary occlusion and myocardial infarction with repeated embolization.

Dr. M. A. Blankenhorn: May we have the report of the morning conference?

Dr. Robert Helm: There were 28 students reporting. All believed that she had thrombophlebitis. Twenty-three students thought that she had multiple arteriolar emboli to the legs and then carried to the kidneys and to the brain and possibly even to the anterior spinal artery. Of these 23, twenty sug-

gested that the source of these emboli was a mural thrombus with a posterior infarction. Other sources brought up during the meeting were bacterial endocarditis, subacute, patent foramen ovale with paradoxical embolism from the thrombophlebitis and sub-endocardial fibrosis with mural thrombus. However, none of these diagnoses were adhered to finally. Four thought that the patient had multiple thromboses without the thromboses being on an embolic basis. One thought that the whole picture could be explained by periarteritis nodosa. A dissecting aneurysm was also discussed but not accepted. As far as renal disease, 27 felt that she had pyelonephritis, 8 thought that perhaps septicemia accompanied this. One voted for necrotizing papillitis and felt that she may have had diabetes on the basis of her last cerebrospinal fluid examination when a blood sugar determination was not done. Sixteen thought that she had renal infarct, and one thought the kidney disease was due to periarteritis nodosa. As far as the pulmonary disease was concerned, 22 believed she had pneumonia and 6 pulmonary infarction.

Dr. Stead: Not a single diagnosis of parasitic infestation!

Dr. Blankenhorn: Dr. Stead, you did not have the benefit of the roentgen study.

Dr. Emanuel Levin (showing films): We see that there is a marked radiolucency between the two lung fields. There is a shelf-like defect in the pulmonary artery. This picture has been described in pulmonary artery embolism.

Dr. Stead: I don't think there is any doubt that that represents occluded pulmonary arteries.

Dr. Blankenhorn: That picture was ascribed to asymmetrical positioning in the protocol.

Dr. Levin: Yes, there is a degree of rotation here and this may result in radiolucency on one side as would be the case here. This decision would favor a slightly greater degree of radiolucency on the left than we see on the right. I think the possibility of a pulmonary artery embolism should have been mentioned by the radiologist in this case. There is, in addition, a slight degree of enlargement of the heart.

Dr. Blankenhorn: May we have the diagnostic report from the Service?

Dr. J. R. Wilson: At death the diagnoses were: phlebothrombosis of the leg, embolization to the kidney, the right side of the brain and lung, and both axillary arteries; cardiac decompensation; right lower lobe pneumonia; and pyelonephritis.

Dr. Edward A. Gall: May I ask a pathological question? In one of his early statements Dr. Stead said that in the absence of a shunt mechanism, certain situations might be considered. When did he exclude the shunt mechanism?

Dr. Stead: The shunt could not have been large because of the fact that she was 76 years of age and she had no signs of a large interatrial septal defect. One would have to assume a rather small hole which wasn't very important except at such time as these emboli began to traverse it. If you wish, you could reason that she had pulmonary embolization, that she began to have an increase of pressure in the right side of the heart and, associated with that, to shunt blood through from the right to the left side of the heart. This is an uncommon situation. It has been reported and does occur. I have never seen it and I didn't think it happened here.

Discussion of Pathology

Dr. Paul Wozencraft: The terminal event was massive bilateral pulmonary embolism as a basis for which thrombi were found in the right popliteal and left deep femoral veins. Two infarcts in the lower lobe of the left lung were evidence of previous pulmonary embolism.

Patency of the foramen ovale was demonstrated by probe and the overlapping margins of the foramen could be spread apart to form an opening about 1 cm. in diameter. As a rule this structure remains closed, as long as the pressure in the left atrium remains higher than that of the right, but with higher pressure in the right atrium, the potential communication is forced. Thus blood and thrombi can pass from the right side of the heart to the left side.

In this instance pulmonary embolism was a reasonable basis for increased pressure in the right heart. An apparent consequence was a folded embolus in the right renal ar-

tery, and the kidney showed many areas of infarction of varying ages. There was also hemorrhagic infarction of the spleen. We believe that these emboli arose in the popliteal or femoral veins, passed up the vena cava to the right atrium, through the foramen ovale to the left atrium, thence into the greater circulation. No lesions were found on the heart valves or mural endocardium to serve as a source for these emboli. No acute infarction was found in the heart, but an area of fibrosis, interpreted as healed infarction, was present. There was no evidence of myocarditis. Bilateral acute pyelonephritis was also found, more severe on the left.

The autopsy was done 9 hours after death. The brain weighed 1120 grams. The dorsal surface of the brain showed congestion of all of the vessels. The veins were tremendously widened and apparently thrombosed at their junctures with the superior longitudinal sinus. The leptomeninges appeared to be normal as did the development of the various gyri. On section of the superior longitudinal sinus it was found to be completely thrombosed. Thrombosis extended into the right sigmoid sinus and into the right internal jugular vein where it terminated just above the jugular bulb. However, there was no thrombosis in the left sigmoid sinus or in the left internal jugular vein. The thrombosis in the superior longitudinal sinus was firm and adherent as was also the case in the right sigmoid sinus and internal jugular vein. There was extension of the thrombotic process into the arachnoid and cerebral veins contiguous to the longitudinal sinus. The arteries comprising the circle of Willis appeared quite normal except for slight thickening.

After fixation the brain was sectioned vertically into blocks 1 cm. in diameter. These sections revealed hemorrhagic infarction of the gyri adjacent to the superior longitudinal sinus. The hemorrhagic infarction was rather symmetrical in the two hemispheres, although that of the right superior frontal gyrus was more extensive than that of the left. Hemorrhagic infarction of the hemispheres continued throughout the posterior sections where the mesial portions of the parietal and occipital lobes on the left were involved massively, whereas that on the right was nowhere near as obvious to the naked eye (Figure 1). Throughout the hemispheres the infarct of the mesial portions involved all of the grey matter and the immediately adjacent white matter. There was congestion and the frequent appearance of small perivascular hemorrhages scattered throughout the white matter. There was increase in bulk of the white matter which in the right frontal lobe had depressed the anterior horn of the lateral ventricle; in the left occipital lobe, the occipital horn of the lateral ventricle had been depressed to a slightly lower level on the left.

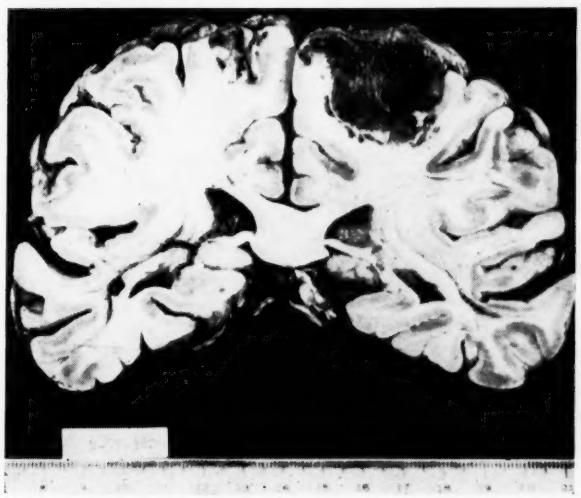

Figure 1. A photograph of a vertical section of the brain through the splenium of the corpus callosum to show the hemorrhagic infarction of the gyri adjacent to the superior longitudinal sinus. In this section the hemorrhagic infarction is quite obvious on the left, and smaller on the right. Also there can be seen a few scattered petechial hemorrhages.

Microscopically there was some inflammatory reaction around the veins containing the thrombi and in the leptomeninges immediately adjacent thereunto. The leptomeninges not in contact with the veins did not contain inflammatory elements. There was acute thrombophlebitis of the cerebral and of the leptomeningeal veins. The multiple hemorrhagic infarcts noted grossly also were seen microscopically. Perivascular hemorrhage and petechial hemorrhages were numerous throughout the brain substance (gray and white matter) and there was beginning necrosis adjacent to many of these hemorrhages.

The changes just described are charac-

teristic of thrombosis of the superior longitudinal sinus. There was no evidence whatsoever of arterial embolization in the brain. We were unable to explain the origin of the venous thrombi. All of the air sinuses and the middle ears were examined and found to be normal.

The presence of unexplained venous thrombosis in widely separated areas has been termed as migrating thrombophlebitis.[1,2] However, a feature is lacking in this case, namely venous thrombosis in the viscera.

Clinical Diagnosis

Phlebothrombosis of the right lower extremity with emboli to the right side of the brain, the kidney, lung and the axillary arteries.

Bronchopneumonia.

Pyelonephritis.

Dr. Stead's Diagnosis

Trichinosis.

Anatomical Diagnosis

Thrombosis of the superior longitudinal sinus, right sigmoid sinus and right jugular vein.

Massive bilateral pulmonary embolism.

Patent foramen ovale.

Paradoxical embolism to right kidney and spleen.

Thrombosis of right popliteal and left deep femoral veins.

Dr. Blankenhorn: Was there actually phlebothrombosis in the lower saphenous circulation?

Dr. Wozencraft: Yes.

Dr. Stead: The cause of death was the terminal pulmonary embolus?

Dr. Wozencraft: I think that was the final blow.

Dr. Gall: Were there parasites?

Dr. Wozencraft: We did not find any.

Dr. Stead: My difficulty did not lie in not knowing she had infarcts in the lung. I knew that. I also knew that she had arterial occlusions. I just didn't believe the arterial emboli were venous clots coming through an open foramen ovale.

Dr. Blankenhorn: Will the pathologist tell us about the factors which opened the foramen in this case?

Dr. Wozencraft: The opening lies in the upper portion of the fossa ovalis. As long as the pressure in the left atrium is higher than that on the right the overlapping remnant of the septum primum is forced against the limbus and the foramen is closed. Higher pressure in the right atrium forces it away from the limbus, opening the foramen. If one probes the foramen routinely he will find some degree of probe patency in a number of cases, probably 30 to 40 per cent.

Dr. Carl Vilter: Would Dr. Wozencraft tell us whether the size of the embolus in the lung was greater or less than the size of the aperture?

Dr. Wozencraft: The embolus in the lung does not have to go through the foramen. The embolus in the renal artery was of a size that could very well pass through the aperture.

Dr. Richard Vilter: I'd like to ask Dr. Blankenhorn how frequently one may expect to hear a murmur when a foramen ovale becomes patent as in this patient?

Dr. Blankenhorn: I have no opinion based on experience. I wouldn't expect a murmur, though I think that the movement of blood might be so slight in such a situation that no sound would reach the ear.

Dr. Iglauer, I'd like to ask how quickly after pulmonary hypertension develops from pulmonary embolization, are signs to be found in the electrocardiogram? What are the circumstances that make them appear quickly and those that may delay them?

Dr. Arnold Iglauer: I don't know the exact answer; but they are found quite early, as early as one can get a tracing.

Dr. Morton Hamburger: Were there any morphological changes to suggest that this patient may have had pulmonary hypertension prior to the pulmonary emboli?

Dr. Wozencraft: It was minimal. The heart weighed 390 grams which is a bit enlarged. The thickness of the left ventricle was 18 mm; the right ventricle was 4 mm. I don't think there was much in the lungs to account for a chronic pulmonary hypertension.

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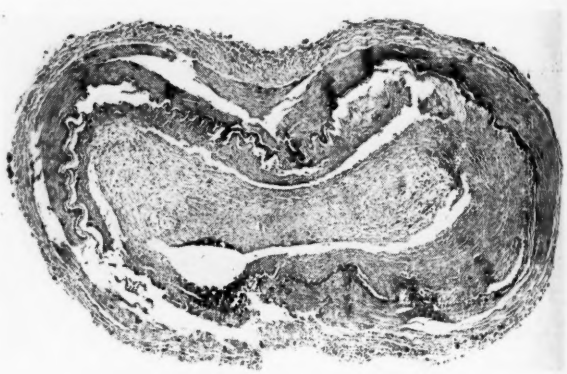

Correction: The figure on page 60 of the February issue was mistakenly published in place of that appearing above, to illustrate the Neurological Clinical Pathological Conference Case No. 281588.

TRANSACTION OF THE GALVESTON NEUROLOGICAL SOCIETY

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RECENT ADVANCES IN THE THERAPY OF HEPATO-LENTICULAR DEGENERATION

IRVIN M. COHEN, M.D.*

MEETING MAY 2, 1952

Since the recognition of hepato-lenticular degeneration as a clinical entity by Kinnier Wilson in 1912,[1] continued efforts have been made to understand the unique pathology of the disease. Many hypotheses have been advanced to explain the simultaneous existence of pathology in the central nervous system and digestive system, but none have satisfactorily explained all the phenomena observed.

Widely varying theories have been suggested. The most prominent have been that it is the result either of a developmental error or a spreading enterotoxin. More recent work tends to suggest rather that it is of metabolic origin, specifically relating to the deposition of copper.

Ordinarily considered a trace element, excessive amounts of copper have been found in the liver and basal ganglia of patients dying of this disease. In 1949 Porter noted excretion of large amounts of copper in the urine and symptomatic improvement with the administration of BAL (2-3 dimercaptopropanol), a drug having the capacity to combine with certain of the heavy metals.[2] In 1951 Denny-Brown and Porter confirmed this initial impression.[3]

The purpose of this presentation is to offer a preliminary report on experience with BAL, and a new antispasmodic drug, 1-Phenyl-1-cyclopentyl-3-piperidine-1-propanol hydrochloride. This experimental drug, labeled Compound 08958 by its manufacturer, is an atropine-like compound, a close relative of Artane, but evidencing the possibility of fewer side effects.

Case Presentations

Patient A had manifested clinical signs of Wilson's Disease for approximately three years. A sister had died at the age of ten years of "cirrhosis of the liver." A brother underwent splenectomy following a diagnosis of Banti's Syndrome. Our patient received a course of BAL according to the suggested schedule of Denny-Brown, and showed moderate but unsustained improvement. Urinary copper excretion determinations parallel those of previous investigators.

Patient B had been ill for 2½ years and was totally disabled by tremor and ataxia. Muscular rigidity was present in mild degree. He showed remarkable improvement following administration of Compound 08958 to the extent that he is now able to walk unaided, tremor is markedly diminished, and he is nearly capable of feeding himself. Regrettably urinary copper determinations were not possible in this patient. Significant improvement took place only after a total of 150 mgm. had been given.

Discussion

Dr. Cohen: The results of the experimental use of Compound 08958 are interesting. The atropine-like drugs are thought to exert their effect by reaction with acetylcholine at the basal ganglia and motor end-plate levels. The effect is transient since such drugs are rapidly excreted. Yet, with Compound 08958 improvement began to take place only after a comparatively large total quantity had been administered. Therefore, the suggestion is made that other mechanisms may be involved.

Dr. Murray: The pathological lesions of Wilson's Disease are found primarily in the basal ganglia and particularly in the lenticular nuclei. Other lesions are also noted in the cerebellum and in the cortex but these appear to a lesser degree. How then might we explain the clinical findings in this disease where cerebellar dysfunction and psychoses are often impressive?

Dr. Schadewold: It appears that the question of cerebellar symptoms appearing in the course of Wilson's disease is entirely consistent with our knowledge or partial knowledge of the anatomy of the pre-rubral, infra-pallidal and medial pallidal connections. We know that projection fibers from the dentate nucleus of the cerebellum extend beyond the red nucleus to the fields of Forel and to the areas mentioned above. Frequently, the lesions in Wilson's disease are not limited to the lenticular nuclei but expand and could conceivably include these fibers emanating from the cerebellum.

Symptoms of organic cortical involvement can likewise be easily explained by the fact that cystic degenerative lesions not unlike those seen in the lenticular nucli are to be found in the fibers immediately subjacent to the cerebral cortex. Several recent papers superbly describe these disseminated foci of the cortical fiber destruction.

Since copper metabolism seems to be implicated in the etiologic or perhaps symptomatic picture in this disease entity, perhaps it would be well to consider those enzyme systems of the brain which are specifically "poisoned" by excesses of copper. One such enzyme, phosphoglucomutase, comes to mind since this enzyme is sensitive to a number of metallic ions among which is copper. Furthermore, this sensitivity is dependent on the -SH groups and is reactivated after copper poisonings by such reducing agents as cysteine and glutathione. The use of BAL further stimulates interest in this system as a possible theory of causation.

Dr. Cohen: I do not believe that symptomatic improvement following heavy copper excretion is prima facie evidence that this disease is exclusively one of faulty copper metabolism. For example, an alpha-aminoaciduria also exists which is unaffected by the administration of BAL. Thus it would appear that copper is but one facet of a more complex disease process.

*Assistant Professor of Neurology & Psychiatry, University of Texas, Galveston.

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